Bronchoscopic lung volume reduction

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CHAPTER

4

Determining the role of dynamic hyperinflation in patients with severe COPD

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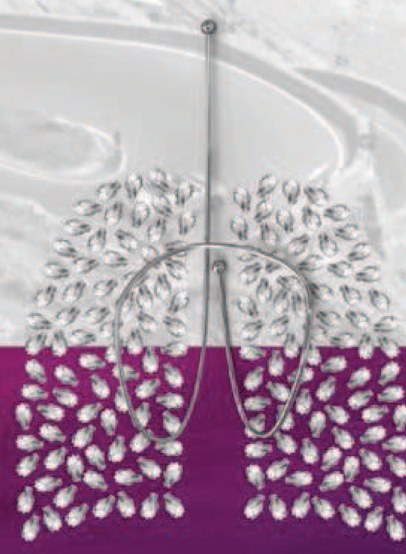

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ABSTRACT

Background
Dynamic hyperinflation due to increased respiratory frequency during exercise is associated with limitations in exercise capacity in patients with moderately severe COPD.

Objectives
The present study assessed whether the manually paced tachypnea test, sitting at rest, induces dynamic hyperinflation correlating with exercise capacity in patients with very severe COPD. Methods: Dynamic hyperinflation was induced by the manually paced tachypnea test, using a breathing frequency of 40 breaths per minute for 1 minute. Dynamic hyperinflation was defined as a 'change' in inspiratory capacity before and directly after the manually paced tachypnea test. At baseline, static hyperinflation by body plethysmography was measured, as well as the 6 minute walk test and spirometry.

Results
We studied 74 patients with severe COPD (age 59±9 years, FEV_1 28±10% of the predicted value). All patients tolerated the manually paced tachypnea test well. It induced a significant decrease in inspiratory capacity of –0.65±0.33 Liters, P<0.001, correlating with the distance on 6 minute walk test (rho= –0.246, P=0.034).

Static hyperinflation (ratio of inspiratory capacity to total lung capacity) at baseline correlated stronger with the distance on the 6 minute walk test (rho=0.582, P<0.001). Multiple regression analysis showed that static hyperinflation, but not dynamic hyperinflation, was the only independent predictor of the distance on 6 minute walk test.

Conclusion
In patients with very severe COPD, dynamic hyperinflation measurement by the manually paced tachypnea test is feasible and contributes less importantly to exercise performance than static hyperinflation.

INTRODUCTION

Dyspnea and subsequent limitation of exercise capacity are the hallmark of clinical symptoms in patients with advanced stages of COPD.[1] These symptoms can either be caused by generic factors like anxiety, muscle weakness and general fitness, or may be due to direct disease related mechanical impairments such as ventilation-perfusion mismatch or reduced lung elastic recoil and increased airway resistance leading to airflow obstruction and subsequent static and further dynamic hyperinflation.[2-7]

Static hyperinflation is defined by an increase in end-expiratory lung volume at rest being accompanied by a decreased inspiratory capacity, the volume from end expiration to full inspiration. In patients with COPD, the elevated resting end-expiratory lung volume is caused by increased airway resistance, due to airway inflammation and airway wall thickening, and/or reduced lung elastic recoil due to alveolar destruction and emphysema. This so-called static hyperinflation correlates well with several important patient-reported outcomes, such as dyspnea, poor exercise performance, and reduced quality of life.[3,4] Static hyperinflation is also an independent risk factor for mortality in subjects with COPD.[8]

Dynamic hyperinflation is defined by a further increase in end-expiratory lung volume associated with elevations in the respiratory rate, as occurs during exercise.[4] Young healthy subjects normally do not show hyperinflation during heavy exercise, but elderly subjects and particularly COPD patients, who have limitations in their expiratory flow rates, may show dynamic hyperinflation during exercise.[7,9,10] In severe COPD, this dynamic hyperinflation is superimposed on top of the already existing static hyperinflation, leading to a significantly reduced inspiratory capacity. This cumulative process of hyperinflation particularly takes place during exercise, as severely obstructed patients mainly increase their minute ventilation by increasing their breathing frequency. The increases in breathing frequency, and thus shortened expiratory time, associated with exertion in the setting of expiratory flow limitation results in progressively increasing hyperinflation, a vicious cycle leading to ventilatory limitation during exertion.[11,12]

Dynamic hyperinflation can be measured by performing inspiratory capacity maneuvers during a cycle ergometry test, but this test requires logistics, is time consuming and, most importantly, is uncomfortable for patients,[13] especially for those with very advanced stages of COPD. An alternative method to investigate the pathophysiology of dynamic hyperinflation, the so-called manually or metronome paced hyperventilation or tachypnea test, can be performed by applying a mandatory tachypnea for a short period while sitting at rest.[14,15] This test is designed to mimic the dynamic respiratory pattern that occurs during exertion, without the inconvenience of putting the subject through a progressive exercise maneuver.[12]

To date, the paced tachypnea test to investigate dynamic hyperinflation has been used predominantly in patients with mild-to-moderate COPD. The present study was designed to investigate the feasibility of the manually paced tachypnea test in patients with more severe COPD and to determine the relationship between dynamic hyperinflation and exercise capacity as assessed by the 6 minute walk test as well as quality of life.

METHODS

Study Design and Population

This was a single-center prospective cohort study in patients with severe COPD who were being evaluated for bronchoscopic lung volume reduction treatment at the Pulmonary Department of the University Medical Center Groningen, the Netherlands. All subjects were clinically stable, on optimal medication, had stopped smoking at least 6 months before the study and participated in one of our bronchoscopic lung volume reduction trials (clinical trial identifiers: NCT01421082; NCT01101958; NTR2876), which were approved by the local ethics committee, and all gave written informed consent.

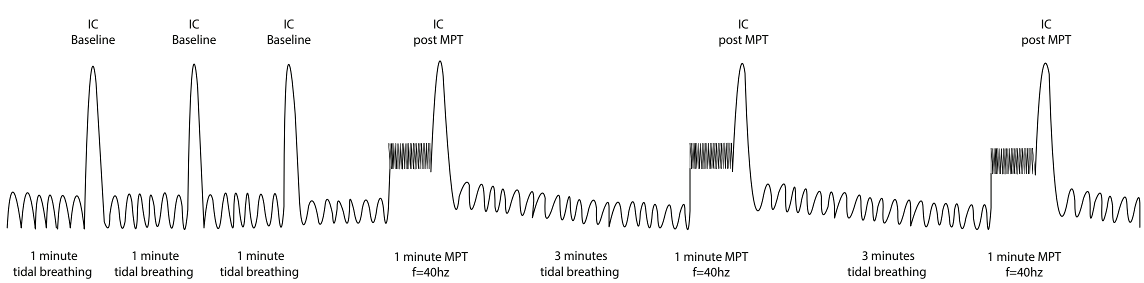
Measurements

The subjects were instructed to use their regular medications, and an additional 400 µg of salbutamol was administered 15 minutes before the pulmonary function measurements. Spirometry, body plethysmography and diffusion capacity were measured using the Jaeger MasterScreen™ body plethysmograph (CareFusion, Germany) and were performed according to the ATS/ERS guidelines[16,17] using the reference values from the European Community for Coal and Steel workers.[18] The 6 minute walk test was done according the ATS recommendations.[19] Quality of life and symptoms were measured using the St. George's Respiratory Questionnaire (SGRQ)[20,21] and the modified Medical Research Council dyspnea scale (mMRC), respectively.[22]

Measurement of Dynamic Hyperinflation

Dynamic hyperinflation was measured using a manually paced tachypnea test with the breath-by-breath method (Oxycon Pro™, CareFusion, Germany) during a 15 minute protocol (see figure 1 for a schematic overview of the manually paced tachypnea measurement).

Figure 1. Schematic overview of the manually paced tachypnea measurement.



f = Frequency (40 times in 1 minute); MPT= manually paced tachypnea test.

The subjects were given a demonstration to familiarize them with the pacing protocol. During tidal breathing, the subjects were asked to perform at least 3 slow maximum inspirations (inspiratory capacity maneuver) with a 1 minute rest in-between each. The technician then coached the subjects to increase their breathing frequency to a rate of 40 times per minute for 1 minute. The subjects were provided vocal feedback of their breathing frequency by the technician who used a computer screen displaying real-time registration of the breathing frequency. Immediately following 60 seconds of tachypnea, the subjects performed an inspiratory capacity maneuver and resumed resting tidal breathing. The manually paced tachypnea (MPT) procedure was repeated at least 3 times with a 3 minute period of resting tidal breathing between maneuvers. To obtain the baseline inspiratory capacity (IC_baseline), we calculated the mean value of 3 reproducible inspiratory capacity values (within 150 ml), and to establish the inspiratory capacity following tachypnea (IC_MPT), we calculated the mean value of the 2 highest and reproducible inspiratory capacity values (within 150 ml).[16] Pulmonary function measurements, questionnaires, 6 minute walk test and the manually paced tachypnea test were all performed on the same day.

Statistics

Data were expressed as means ± standard deviation unless otherwise indicated. A P value of <0.05 was considered statistically significant. To evaluate the variability in the repeated inspiratory capacity measurements (IC_baseline and IC_MPT), a variation coefficient was obtained by dividing the standard deviation of the inspiratory capacity measurements by the individual mean. A difference of <10% was accepted. Static hyperinflation was expressed by IC_baseline in proportion to the total lung capacity assessed by body plethysmography, thereby assuming that the total lung capacity remains constant during the manually paced tachypnea test.[10,23] Dynamic hyperinflation was calculated by the absolute change in inspiratory capacity (IC_MPT minus IC_baseline) as well as the difference (IC_MPT/total lung capacity minus IC_baseline/total lung capacity).[8] The Wilcoxon signed-ranks test was used to compare IC_baseline and IC_MPT and to compare IC_MPT/total lung capacity and IC_baseline/TLC. Pearson correlation was used to investigate univariate associations between static hyperinflation or dynamic hyperinflation and pulmonary function variables, exercise performance and quality of life when data were normally distributed. In case of non-normal distribution, Spearman correlation was used. Univariate associations with a P value <0.15 were entered in the multiple regression model. Highly correlating variables (correlation coefficient >0.75) were not entered in the model. The change in inpiratory capacity and the ratio of inspiratory capacity to total lung capacity (IC/TLC) results from the literature, shown in table 5, were either directly taken from the papers, or recalculated using the available input from these papers. IBM SPSS Statistics version 22 (IBM; Armonk, N.Y., USA) was used for all analyses.

RESULTS

Patient Characteristics

Seventy-four clinically stable patients with severe COPD (FEV_1 28±10% of the predicted value) were included between May 2010 and July 2012 (see table 1 for demographics and baseline characteristics). All subjects tolerated the manually paced tachypnea test well and were able to maintain a manually paced rate of 40 per minute (range 36–43) for 1 minute during all attempts (see table 2 for dynamic hyperinflation measurement characteristics).

Table 1. Patient demographics and baseline characteristics (N=74).

Characteristic	
Male/Female	25/49
Age, years	59±9
Smoking history, pack years	39±16
BMI, kg/m2	23.7±3.5
BODE index (N=73)	5.4±1.5
FEV1, Liter	0.77±0.32
FEV1, % of predicted value	28±10
FVC, Liter	2.53±0.83
FVC, % of predicted value	75±7
Ratio of FEV_1 to FVC, %	31±7
RV, % of predicted value	233±49
TLC, % of predicted value	136±14
Ratio of RV to TLC, %	62±9
Raw, kPa/Liter/second	0.73±0.28
Raw, % of predicted value	245±94
DL_{CO}, mmol/minute/kPa (N=63)	3.31±1.13
DL_{CO}, % of predicted value	38±12
Distance on 6 minute walk test, meter	357±92
SGRQ, points (N=73)	60.3±13.6
mMRC, points (N=73)	2.8±0.8

Results are presented as means ± standard deviation or numbers. FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; Raw = airway resistance; DLCO = carbon monoxide diffusion capacity.

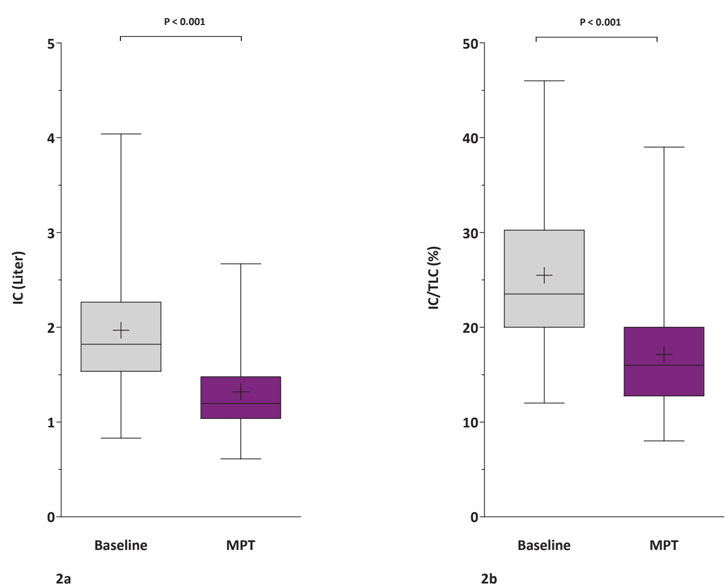
Table 2. Dynamic hyperinflation measurement characteristics (N=74).

Variables	Baseline	During MPT	P value
Breathing frequency, breaths/minute	16 (8 to 27)	40 (36 to 43)	<0.001
Tidal volume, Liter	0.75 (0.4 to 1.4)	0.54 (0.34 to 1.53)	<0.001
Ventilation, Liter/minute	12 (6 to 24)	21 (13-61)	<0.001
End tidal carbon dioxide fraction, %	4.67 (2.70 to 7.19)	3.69 (1.92 to 6.14)	<0.001
Ratio of inspiration to total time, %	34 (21 to 58)	40 (32 to 58)	<0.001

Results are presented as median (range). Difference between baseline and during manually paced tachypnea were measured with paired T-test. MPT= manually paced tachypnea.

The repeated inspiratory capacity maneuvers to establish IC_baseline and IC_MPT were reproducible showing a mean ± standard deviation variation coefficient of 4.7±0.1% and 4.3±0.1%, respectively. Immediately after the 60 seconds of tachypnea, we measured significantly lower inspiratory capacity values in all patients. In the total group, IC_baseline was 1.97±0.62 Liter and IC_MPT was 1.32±0.5 Liter. The absolute change from baseline in inspiratory capacity was –0.65±0.33 Liter(P<0.001; figure 2a). IC_baseline/TLC was 25.5±7.5% and IC_MPT/TLC was 17.1±6.2%. The absolute change from baseline in IC/TLC was –8.4±4.3% (P<0.001; figure 2b).

Figure 2. Manually paced tachypnea test results of dynamic hyperinflation.



Results presented in boxplots: median (horizontal line) and mean (+); whiskers: range. **2a.** Inspiratory capacity (IC) at baseline and directly after the manually paced tachypnea test. **2b.** Ratio of inspiratory capacity to total lung capacity (IC/TLC) at baseline and directly after the manually paced tachypnea test (MPT).

Table 3 shows the univariate associations of static hyperinflation and dynamic hyperinflation with pulmonary function tests, quality of life and exercise performance.

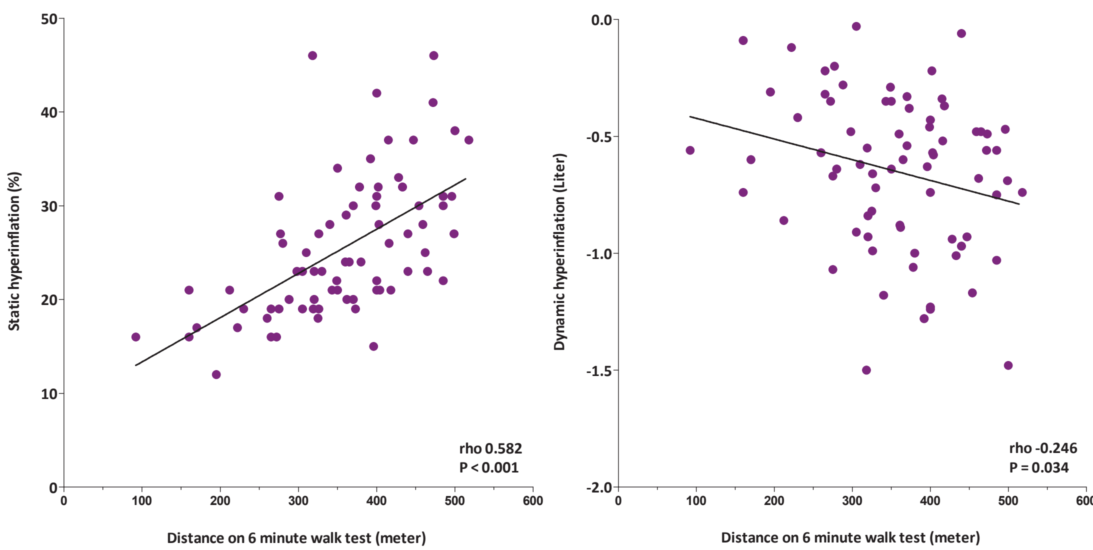
Table 3. Univariate associations between static hyperinflation and dynamic hyperinflation with pulmonary function, quality of life and exercise performance.

Variable	Static hyperinflation	P Value	Dynamic hyperinflation	P Value
VC, Liter	0.583	<0.001	-0.495	<0.001
FEV_1, Liter	0.724	<0.001	-0.343	0.003
FEV_1, % of predicted value	0.711	<0.001	-0.212	0.070
Ratio of FEV_1 to FVC, %	0.415	<0.001	0.008	0.948
RV, % of predicted value	-0.714	<0.001	0.143	0.226
TLC, % of predicted value	-0.492	<0.001	0.019	0.872
Static hyperinflation	-	-	-0.489	<0.001
Raw effective, kPa/Liter/second	-0.598	<0.001	0.182	0.121
DLCO, mmol/minute/kPa	0.399	0.001	-0.379	0.002
VE_MPT, Liter/minute	-0.612	<0.001	-0.323	0.005
6MWD, meter	0.582	<0.001	-0.246	0.034
SGRQ, points	-0.285	0.015	0.091	0.443
mMRC, points	-0.499	<0.001	0.195	0.097

Static hyperinflation: IC_baseline/total lung capacity, %; Dynamic hyperinflation: IC_MPT minus IC_baseline, Liter; VC = vital capacity; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; Raw = airway resistance; DLCO = carbon monoxide diffusion capacity; VE_MPT = ventilation during manually paced tachypnea.

Static hyperinflation as expressed by the ratio of the inspiratory capacity at baseline to total lung capacity was associated with a shorter distance on the 6 minute walk test (rho=0.582, P<0.001; figure 3a) as well as with worse quality of life (SGRQ; rho= –0.285, P=0.015) and greater severity of dyspnea (mMRC; rho=–0.499, P < 0.001). Dynamic hyperinflation as defined by change in inspiratory capacity was associated with a longer distance on the 6 minute walk test (rho= –0.246, P=0.034; figure 3b), but no association was found with quality of life.

Figure 3.

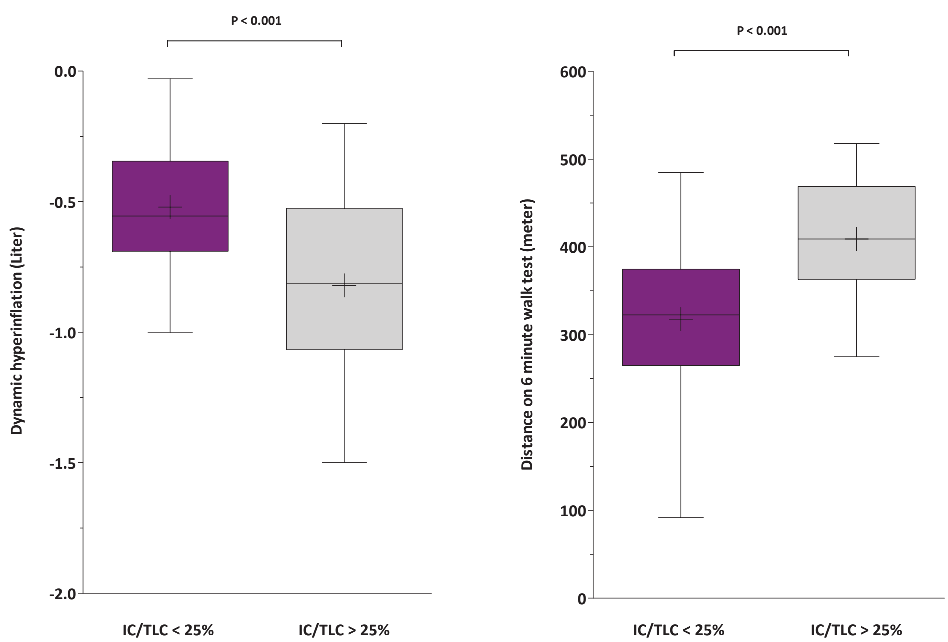


3a **3b**

Static hyperinflation **(a)** and dynamic hyperinflation **(b)** associated with exercise capacity. Static hyperinflation: IC_baseline/TLC; Dynamic hyperinflation: IC_MPT minus IC_baseline.

Subjects with less severe static hyperinflation (defined as an IC_baseline/TLC ratio of >25%) showed significantly more dynamic hyperinflation, thus a greater change in inspiratory capacity (–0.82±0.35 Liter) compared to subjects with more severe static hyperinflation (defined as an IC_baseline/TLC ratio of <25%; with a change in inspiratory capacity of –0.52±0.25 Liter, P< 0.001; figure 4a). The distance on 6 minute walk test was longer in subjects with less severe static hyperinflation (distance on 6 minute walk test 409±68 meter), compared to subjects with more severe static hyperinflation (distance on 6 minute walk test 318±89 meter; P<0.001; figure 4b).

Figure 4. Comparison of IC/TLC <25% versus IC/TLC >25% with dynamic hyperinflation and the distance on 6 minute walk test.



4a

4b

Results presented in boxplots: median (horizontal line) and mean (+); whiskers: range. Dynamic hyperinflation: IC_MPT minus IC_baseline. (**a)** Dynamic hyperinflation in subjects with IC_baseline/TLC <25% compared to subjects with IC_baseline/TLC >25%. (**b)** Distance on 6 minute walk test in subjects with IC_baseline/TLC <25% compared to subjects with IC_baseline/TLC >25%.

The multiple regression analyses showed that the IC_baseline/TLC ratio (static hyperinflation) as well as vital capacity were independent predictors of dynamic hyperinflation (change in IC) and that static hyperinflation (IC_baseline/TLC ratio) was the only independent predictor of the distance on 6 minute walk test (table 4).

Table 4a. Multiple linear regression analyses with dynamic hyperinflation as dependent variable.

	dependent variable:	**dynamic hyperinflation**	
variable	**B**	**Standard error**	**P Value**
Vital capacity, Liter	-0.189	0.086	**0.032**
FEV_1, Liter	0.371	0.203	0.072
Static hyperinflation	-0.026	0.007	**<0.001**
Raw effective, kPa/Liter/second	0.371	0.203	0.072

Table 4b. Multiple linear regression analyses with the distance on 6 minute walk test as dependent variable.

	dependent variable:	**6MWD**	
variable	**B**	**Standard error**	**P Value**
Vital capacity, Liter	0.334	25.106	0.150
FEV_1, Liter	-0.045	58.609	0.828
Static hyperinflation	0.402	2.145	**0.024**
Raw effective, kPa/Liter/second	-0.111	46.362	0.493
Dynamic hyperinflation	-0.108	34.670	0.390

Analyses were adjusted for age, height and sex. Dynamic hyperinflation: IC_MPT minus IC_baseline. Static hyperinflation: IC_baseline/TLC. FEV_1 = forced expiratory volume in 1 second; Raw = airway resistance.

DISCUSSION

We demonstrate good feasibility for the use of the manually paced tachypnea test to induce dynamic hyperinflation in a group of patients with severe COPD. As expected, static hyperinflation was strongly associated with dyspnea rating, quality of life, several pulmonary function outcomes and poor exercise performance. While dynamic hyperinflation was associated with both dyspnea and exercise tolerance, contrary to what had been found in more mild COPD populations, there was no association with dyspnea severity or quality of life in our population. This indicates that subjects with more preserved airflow obstruction and less static hyperinflation had more dynamic hyperinflation, which was associated with better exercise capacity.

Dynamic hyperinflation was tested using the manually paced tachypnea test. The protocol used in this study was based on previously published metronome paced tachypnea protocols.[13,14,15,24] Instead of using the metronome, we chose to instruct these severe patients more personally by the technician supported by real-time monitoring of the breathing frequency. Using this approach, we achieved an average breathing frequency of 40 breaths per minute with a very small variation in the actual frequency (range 36–43 breaths per minute). Metronome or manually paced tachypnea measurements may mimic the ventilatory pattern during an exercise test in patients with severe airflow obstruction. Indeed, tidal volumes decreased during the paced tachypnea test with increasing breathing frequency being responsible for the augmentation in minute ventilation.[11,12] Although the paced tachypnea test does not exactly reflect exercise pathophysiology in this patient group, with our approach, using the manually paced tachypnea test, we achieved an average decline in inspiratory capacity of –0.65 Liters indicating that our manually paced tachypnea test is an appropriate method to test for dynamic hyperinflation.

Previous metronome paced tachypnea studies using protocols with a tachypnea period between 20 and 60 seconds and a breathing frequency of 40 breaths per minute,[13,14,15] or two times the resting breathing frequency,[2,25,26] also achieved a decline in inspiratory capacity (table 5). All previous studies were performed in a population of patients with a mainly moderate severity of COPD, and with very few severe COPD patients as represented in our study. The results in table 5 show that the magnitude of dynamic hyperinflation is hardly related to the degree of airflow obstruction, although it is problematic to compare changes in inspiratory capacity between studies, given subtle differences in the protocol and respiratory patterns achieved. Studies enrolling patients with an average FEV_1 of 1.86 Liter (65% of predicted value)[26] showed the same change in inspiratory capacity of –0.54 Liter compared with studies enrolling patients with an FEV_1 of 1.22 Liter (43% of predicted value).[14] In our population with patients who have more severe airflow obstruction, with an FEV_1 of 0.77 Liter (28% of predicted value), we even found a greater change in inspiratory capacity (–0.65 Liter). Table 5, in addition, shows that our study included patients with the lowest ratio of inspiratory capacity to total lung capacity at baseline, reflecting worse static hyperinflation.

Table 5. Literature overview of previous studies investigating the paced tachypnea test.

Author	Paced Tachypneu Method	N	FEV_1, Liter	FEV_1, % of predicted value	Ratio of IC to TLC, %	Delta IC, Liter
Hannink[25]	2 x BF rest	68	1.61±0.07	56±2	-	-0.62±0.04
Lahije[26]	2 x BF rest	45	1.86±0.73	65±24	37*	-0.54*
Cooper[24]	40 Hz	35	1.76±0.5	59±9	37*	-0.36±0.05
Calligaro[13]	40 Hz	24	1.70±0.45	59±9	37*	-0.37±0.30
Gelb[2]	2 x BF rest	16	1.63±0.53	60*	39*	-0.39±0.29
Lahije[28]	2 x BF rest	53	1.60±0.6	58±22	38*	-0.53*
Fuijmoto[15]	40 Hz	59	-	54*	-	-0.32±0.03
Weigt[14]	40 Hz	14	1.22±041	43±14	30±11	-0.54
Current study	40 Hz	74	0.77±0.32	28±10	25.5±7.5	-0.65±0.33

Data are presented as means ± standard deviation or in numbers. *Standard deviation value is not available. BF = breathing frequency.

How can we explain that our very severe COPD patients revealed the highest change in inspiratory capacity in the literature, yet a negative correlation with disease severity within the study? We hypothesize that dynamic hyperinflation during tachypnea may progress differently with increasing severity of airway obstruction and static hyperinflation. Young individuals without airway obstruction routinely lower their end-expiratory lung volume and thus increase their inspiratory capacity during exertion. By contrast, aging individuals and those who progress from minimally to moderately obstructed will elevate their end-expiratory lung volume and decrease their inspiratory capacity.[23,27,28] Finally, individuals who have progressed to very severe airway obstruction like in our study frequently have an already hyperinflated state at rest. Such individuals have little capacity to further increase their elevated end-expiratory lung volume, and consequently show only modest decreases in inspiratory capacity. In our study, we included mainly very severe COPD patients, and, therefore, we were able to demonstrate a negative correlation between dynamic hyperinflation and disease severity. Future studies might also include a comparative group of less severe COPD patients.

As expected, we found a strong inverse correlation between static hyperinflation and exercise performance.[3,4] Contrary to our expectations, however, we observed that a greater dynamic hyperinflation as reflected by a greater reduction in inspiratory capacity was associated with a longer distance on the 6 minute walk test. This finding contrasts with observations in previous studies, which included mainly moderate COPD patients.[29] These previous studies demonstrated that the presence or magnitude of dynamic hyperinflation was either unrelated to exercise endurance and dyspnea[13,28] or that dynamic hyperinflation was associated with a decline in physical activity.[29] In our population with severe COPD patients, 57% of these patients had a ratio of inspiratory capacity to total lung capacity below 25%,[8] reflecting more severe static hyperinflation.

These individuals thus have very little capacity to decrease their inspiratory capacity even further during the manually paced tachypnea test or during exercise. Interestingly, the distance on 6 minute walk test correlated significantly with both static and dynamic hyperinflation; however, the correlation was stronger with static hyperinflation, and static hyperinflation was the only independent predictor of the distance on 6 minute walkt test in a multiple regression model. We believe that the observed negative association between dynamic hyperinflation and the distance on 6 minute walk test is attributable to the greater disease severity of our population and the associated severe static hyperinflation.

CONCLUSION

The 15 minute manually paced tachypnea test is a feasible procedure to study dynamic hyperinflation in patients with severe COPD. Static hyperinflation in this severe group seems to be a more important contributor to limited exercise performance and poor quality of life than dynamic hyperinflation. Based on the data of this study, static hyperinflation seems to be a better predictor of exercise performance than dynamic hyperinflation. The negative correlation between the static and dynamic hyperinflation reflects the reduced capacity of very severe COPD patients to increase their already elevated static hyperinflation. Measurements of inspiratory capacity or change in inspiratory capacity in this group made during dynamic maneuvers do not further contribute to an understanding of their exercise or functional limitations, in contrast to such observations made in patients with mild and moderate airway obstruction.

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